Problematic placebos in physical therapy trials

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Abstract

The function of a placebo control in a randomised trial is to permit blinding and reduce risk of bias. Adopting Grűnbaum's definitional scheme of a placebo, all treatments must be viewed as packages consisting of characteristic and incidental features. An adequate placebo for an experimental treatment contains none of the characteristic features, all of the incidental features, and nothing more. For drug treatments, characteristic features can be readily identified, isolated, and separated. By contrast, physical therapy treatments often involve features such as patient-therapist contact and sensory feedback that make this separation difficult both conceptually and practically. It is therefore unsurprising that attempts to construct placebos for physical therapy treatments have in the past led to biased estimates of treatment effects. In this perspective piece, we describe the problem with constructing placebos for physical therapy trials drawing upon Grűnbaum's definition and using paradigmatic examples from existing literature. We conclude by submitting that in the many cases where an adequate placebo cannot be achieved, alternative trial designs, e.g. dose-response or comparative-effectiveness trials, carry a lower risk of bias and should be favoured.

Keywords: physiotherapy, placebos, randomised trial, research methodology, science

The placebo control

The placebo controlled, randomised controlled trial is widely recognized as the gold standard design for providing evidence in health care [1]. Yet controversies surrounding placebos persist, which include issues regarding ethics [2], legality [3], mechanisms [4], and even whether there should be such a thing as placebo at all [5]. Here, we intend to highlight some of the difficulties in the design and use of placebo controls within physical therapy trials. Unlike placebo tablets, which can be constructed simply by removing the active or 'characteristic' ingredient, physical therapy treatments are often more complex, with many active features that cannot be easily separated. Based on the challenges of isolating the characteristic feature(s) of treatments, we explore the problem with constructing placebos in trials of physical therapies, drawing on philosophy of science as a basis for defining what a placebo is and is not. After pointing out common problems, we outline potential solutions using alternative designs that allow trials to remain rigorous, while at the same time avoiding the pitfalls introduced when using inadequate placebos.

The primary function of a placebo control in a randomized trial is to blind investigators and patients so that they do not know which treatment they receive. This reduces the confounding effects of expectations, from the participant and others, and thus reduces bias [1,5]. Although the purpose of placebos is widely understood, they have proved rather difficult to define. Flawed definitions have included 'an inactive or inert intervention' [6], 'a treatment that has not been proved effective' [7], and anything 'offered to mimic the treatment being tested' [8]. Placebos are of course not inert, having proven effects [9], and recent neuro-psychological studies reveal a great deal about the mechanisms through which placebos act [10]. Including a broad statement on effectiveness in the definition of a placebo

is a mistake, as clearly the same treatment will act differently on different outcomes, and proof of effectiveness on any outcome can change over time (with emerging evidence) - so a placebo can become a treatment and vice versa. Philosophically, we submit that Grűnbaum [11,12] offers the most operationally useful conceptualization of placebo. His account requires that all treatments, however simple, must be viewed as packages consisting of characteristic and incidental features. Which features are seen as characteristic and which incidental is relative first to the indication for that treatment, and second to the therapeutic theory of the people involved in giving or receiving it. To offer illustrative examples, the glucose in a sugar pill might be considered characteristic if it was being used to treat hypoglycemia, but incidental in many other cases. Regarding therapeutic theory, the insertion of an acupuncture needle at the correct point along a 'Qi' might be characteristic, but this depends on which theory is followed (see [13] for further detail). Once the features of a treatment package have been delineated, an adequate placebo control within this definition [11,12] must contain:

1. All of the incidental features of the treatment,
2. None of the characteristic features, and
3. Nothing more.

In drug treatments, the characteristic features are usually readily identified, isolated, and separated. For example, in a Prozac tablet, fluoxetine hydrochloride is the sole characteristic feature and the other features (the tablet casing, bulking agent, liquid with which the tablet is swallowed, etc.) are incidental (Figure 1). In a trial therefore, an adequate placebo control must be constructed from an otherwise similar tablet, offered and consumed in the same way, but not containing fluoxetine hydrochloride. It should look, taste, and feel the same so

that it cannot be distinguished from the experimental treatment and the expectations of the participants (and others) are unchanged [14].

Compared to tablets, the characteristic features of most physical therapy treatments are harder to distinguish both conceptually (what counts as incidental or characteristic?) and practically (how can these features be physically separated?). What would an exercise placebo look like for example? How could something be designed that a trial participant thinks is exercise, but is not? Verbal instruction and education, patient-therapist contact, physical action by the patient or therapist, and sensory feedback all have potentially therapeutic benefit on multiple outcomes, so could be considered characteristic features, but otherwise are extremely difficult to imitate (Table 1). To compound this issue, physical therapy treatments are often more complex than a tablet, involving multiple components treatment that interact with each other. This deepens the problem of separating out characteristic and incidental features which, we argue, puts placebos of physical therapies at high risk of failure. This is important as inadequate placebo controls lead to unblinding, altered expectation, and therefore systematically biased research.

Paradigmatic examples of biased placebos that lead to underestimates of treatment effect sizes

One trial compared the effects of neck manipulation (involving neck movement which includes a joint preload and thrust) with a placebo technique that included therapists moving the neck without preloading and thrusting the joint [15]. The trial showed no difference in pain reduction between the groups, suggesting the treatment to be ineffective. However, there are reasons to believe that the treatment effect was underestimated owing

to the placebo used. The chosen placebo implies that the investigators have classified preloading and thrusting the joint as the only characteristic features of the treatment being tested. Nonetheless, the placebo used manual therapy-type movement and touch, and for both of these there is independent evidence of (non-placebo) effectiveness for treating neck pain [16,17]. This evidence challenges the investigator's classification of these features as incidental. If we are correct, then the 'placebo' controls used in this trial are not adequate 'Grünbaumian' placebos. This is because some characteristic features of the experimental treatment – those with independent evidence of effectiveness – were likely preserved in the placebo, which fails point 2 of Grűnbaum's criteria above. Further, new features were introduced into the placebo with the intent to maintain participant blinding, including a therapeutic table drop-segment and re-developed tissue contact to ensure adequate sensory feedback [15]. When additional features are unintentionally introduced to the placebo it fails to meet point 3 [18]. These features, characteristic or not, are potentially therapeutic in their own right, and could shrink the difference in effect observed between the experimental and placebo conditions. Use of Grunbaum's definition here helps to identify these features as potential confounders, which can assist in the subsequent interpretation of effect estimates.

For our next example, we draw upon two trials that compared the effects of elastic taping with a placebo involving elastic taping in the 'wrong' place [20], or without the required amount of tension [21]. Initially, these trials may be taken as using seemingly well-constructed placebos, but when considered using Grunbaum's definition, the separation of characteristic and incidental features, particularly in relation to the therapeutic theory, is insufficient. The placebo designs used in these trials imply that the characteristic feature of

elastic taping might be its placement [20] or tape tension [21]. However, in both cases the investigators claim that the therapeutic (i.e. characteristic) feature of the tape was its elasticity. Since both trials used elastic tape in the placebo group, the putatively characteristic feature was preserved in the placebo group, thus failing to meet point 2 of the definition. Rather than providing placebo controlled evidence for elastic taping, these trials demonstrate that elastic taping applied in the 'correct' way proved more effective than elastic taping applied 'incorrectly'. In both cases, the presence of the characteristic feature in both treatment and control means that the benefits of *elastic* tape have not been tested – the chosen placebo design was not concordant with the therapeutic theory. This critique might appear academic, but trials using non-elastic tape placebos, which maintain other incidental features, tend to demonstrate a lack of effect [22, 23].

Biased placebos that lead to overestimation of treatment effect sizes

Yet another trial [19] compared the effects of motor control exercises (exercise prescription aimed at improving movement quality) with detuned electrotherapies (inactivated passive therapy units) on recovery and activity in patients with chronic low back pain. The trial showed a large treatment effect, but in this case there is reason to suspect the chosen placebo design led to an overestimate of effectiveness. The justification for detuned electrotherapy as a placebo was established credibility as placebos in other settings. However, Grunbaum's definition clearly entails that the adequacy of a placebo is to be judged against the features of the experimental treatment in question [12]. Electrotherapies bear little resemblance to the motor control exercises being tested, so a participant in this trial would have experienced the characteristic and incidental effects of two altogether different treatments. This placebo control fails because it does not include all the incidental

features of the treatment (point 1), and possess additional features to those of the treatment, characteristic and incidental (point 3). It therefore does not isolate the characteristic effects of the treatment being tested. The failure to use an adequate placebo could have exaggerated the benefits of motor control exercises.

Ways forward when placebos are difficult to construct

The fact that placebos of physical therapies are difficult to define does not imply that we should not conduct randomised trials of physical therapies. However, care must be taken to reduce the bias introduced by 'placebo' controls. Part of the utility of Grunbaum's account of placebos for physical therapy trials is that it requires investigators to explicitly list the characteristic features, relative to the condition and theory, in order to determine what placebos would count as legitimate, and whether these can be realised practically. If a placebo control is used, the placebo label alone is strongly discouraged. We urge investigators to report their chosen placebo in sufficient detail that it can be understood, appraised and replicated [5,24], which would include the procedures used, timing of treatment, and supporting materials such as patient hand-outs [25]. For example, in the taping examples [20,21] enough information is offered to learn that the characteristic feature of the treatment (as understood) remains in the placebo. However, there is remaining uncertainty around potential differences in patient education and instruction. The recent template for intervention description and replication (TIDieR) checklist and guide [26] offers a suitable framework to describe both experimental and placebo interventions.

In cases where an adequate placebo cannot be constructed, investigators might consider alternative trial designs. These could include a dose-response trial in which groups would

receive the same treatment in different amounts [27], or a comparative effectiveness trial, where physical therapy is compared to an established line of treatment, such as optimal medical management [28]. These trial designs cannot be made blind, but unlike with placebo controlled trials, the comparator treatment is not compromised in an attempt to do so [1,18]. It becomes a case of weighing up and balancing potential biases. For example, in trials for patients with low back pain, a comparative effectiveness trial [29] compared (stratified) physiotherapy to (non-stratified) current best practice, whereas the placebo controlled trial compared physiotherapy to a detuned electrotherapy intervention [19]. Whilst the former is not placebo controlled, it offers more clinically useful information; patients, clinicians and policy makers wish to know how a treatment compares with other available options.

In summary, adequate placebos are difficult to achieve within physical therapy trials, often leading to biased estimates of treatment effect. If used, placebos should be fully described so they can be judged against the three-fold criteria of containing; all the incidental features of the treatment; none of the characteristic features; and nothing more. In the many cases where an adequate placebo cannot be achieved, other options at lower risk of bias should be considered in light of probable deficiencies.

Authors contributions

All authors contributed equally to this work.

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Figure 1. Treatments as packages of characteristic and incidental features

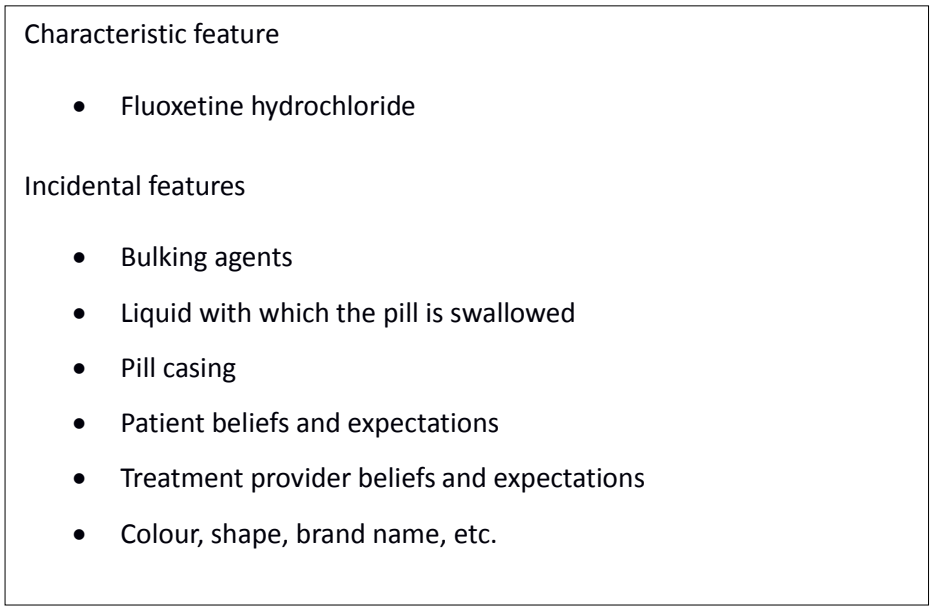

Table 1. Common features of physical therapy treatments that make adequate placebos difficult to construct

		Physical therapy treatment										
		Exercise	Taping technique	Manual therapy technique	Movement facilitation	Advice and education	Acupuncture	Chest clearance technique	Ultrasound /pulse short-wave therapy	Neuromuscular electrical stimulation	Transcutaneous electrical stimulation	Hydrotherapy
Feature of treatment	Includes verbal instruction / education	x	x	x	x	x		x	x	x	x	x
	Includes therapist supervision	x			x							x
	Requires patient-therapist physical contact		x	x	x		x	x	x	x	x	
	Requires physical action by patient	x			x			x		x	x	x
	Requires physical action by therapist		x	x	x		x	x	x	x	x	
	Produces sensory feedback	x	x	x			x	x		x	x	
	Produces physiological response(s)	x		x						x	x	x
	Produces cognitive response(s)	x	x	x		x	x		x			
	Produces expected side effect(s)	x		x			x			x		x